REMARKS/ARGUMENTS

Applicants respectfully request entry of this Amendments and reconsideration of the instant claims. Applicants also file herewith a Request for Continued Examination. Applicants arguments address the rejections raised by the Office in the Final Office Action dated August 19, 2008 (hereinafter "OA").

By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 1-5, 7-12, 14-18, 20 and 21 are pending in this application. Claims 6, 13, and 19 have been previously canceled.

Claims 2, 9 and 15 are currently canceled herein.

Claims 1, 7 and 14 have been amended to limit the recited drug to an antihistamine and wherein the composition does not pass into the pulmonary system. Support for the amendments to claims 1, 7 and 14 can be found in the originally filed claims and in paragraphs [0001]-[0014] and the Examples of the specification.

Claim 3 has been amended to correct dependency due to the cancellation of claim 2.

Claim 20 has been has been amended for clarity.

The claim amendments do not introduce any new matter.

35 U.S.C. §103 Rejections

I. Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 have been rejected under 35 USC §103(a) as allegedly unpatentable over Steiner et al. (US 5,503,852, hereinafter "Steiner"). OA, page 2. Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office smust show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

Independent claims 1, 7 and 14 have been amended to indicate that the claimed drug is an antihistamine and that the claimed composition does not pass into the pulmonary system. Claims 2, 9 and 15 have been canceled.

Steiner teaches that microparticles can be used as diagnostics with radiopaque, radiolabeled, radioluscent, magnetic or fluorescent materials to bind to mucosal membranes, "especially for imaging of the nasal and pharyngeal, gastrointestingal, and genitorurinary tracts" (Steiner column 13, lines 14-24). Steiner also teaches that "[i]ntravenous administration of microparticles containing imaging agents are particularly useful for imaging liver, spleen or lung." Id. Steiner does not teach or suggest that the microparticles could be used to deliver drugs to the nasal cavity as therapeutics and

makes no suggestion that the microparticles could be used with antihistamines as claimed herein. Applicant's note that the Office asserted that "Steiner does not explicity teach the selective antihistamines chosen…" (OA, page 5).

Furthermore, contrary to the Office's statement that "Applicants have not demonstrated that the '10 micron' size range claimed is a critical lower limit" (OA, page 4), Applicants have demonstrated through the Examples presented in the specification that 10 microns appears to be the critical lower limit of the particle size. This is evidenced in Example 3 by the results of administration of Formulations I and II in which reduction of bitter aftertaste (particles reaching the back of the mouth and throat) and reduction of somnolescence reported by the test subjects. Therefore, Applicants have established that particles which are predominantly smaller than 10 microns in size, pass through the nasal cavity and into the pulmonary system.

Applicants respectfully point out that Formulations I and II do not comprise a diketopiperazine as does the formulation described and used in the experiments presented in Example 5. Accordingly, the claimed composition and methods comprise microparticles differing from those of Formulations I and II and comprise an antihistamine and a diketopiperazine. Example 5 clearly represents particles comprising an antihistamine and a diketopiperazine and having a size range between 10 and 20 microns in diameter wherein the particles of Examples 1 to 4 comprise antihistamine alone. The particles of Example 5, comprising a diketopiperazine and an antihistamine, and from 10-20 microns in size, did not cause a bitter aftertaste after administration, confirming that they are retained in the nasal cavity.

Applicants provide herewith a publication by one of the instant inventors supporting the statements made herein. Wilson et al. (Respiratory Drug Delivery VIII, 2002; hereinafter "Wilson"), published after the filing of the present application, indicates that particle size is critical in differentiating how the particles can be administered to a subject. The Wilson reference describes how microparticles comprising diketopiperazine can be made for pulmonary versus nasal delivery. This reference demonstrates that it would not have been obvious to one of skill in the art to formulate

microparticles for nasal delivery as presently claimed, using the same method for making fine particles for pulmonary delivery, as taught and suggested by Steiner. As stated on page 545 (last paragraph) of Wilson, the microparticles for nasal administration were made differently than those for pulmonary inhalation. For pulmonary inhalation, and as described in Steiner, the particles were made in a basic aqueous solution. For nasal delivery, the particles were made by dissolving the diketopiperazine in a co-solvent system of water and an organic solvent. There is no teaching or suggestion in Steiner as to how microparticles for nasal delivery of a therapeutically active agent, having the required size to be retained in the nasal cavity, could be made.

Therefore, Applicants respectfully assert that Steiner does not teach or suggest all the claim limitations of pending claims 1, 4, 5, 7, 11, 12, 14, 17 and 18 and request the withdrawal of the rejections on this basis.

II. Claims 3, 8, 10, 16, 20 and 21 have been rejected under 35 USC §103(a) as allegedly unpatentable over Steiner et al. as applied to claims 1, 2, 4, 5, 7, 9 11, 12, 14, 15, 17, and 18 and further in view of Illum (US 5,690,954). OA, page 5. Applicants respectfully traverse.

Claims 3, 8, 10, 16, 20 and 21 claim dependency from claims 1, 7, and 14. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 USC § 112. As discussed *supra*, Steiner does not disclose all the claim limitations of independent claims 1, 7 and 14. Illum does not cure the deficiencies of Steiner.

Illum teaches microsphere particles containing a material which improves the bioavailability of an active drug, i.e., an absorption-enhancing material such as phospholipids and lysophosphatidyl compounds such as lysolecithin, lysophosphatidyl enthanolamine, lysophosphatidyl glycerol, lysophosphatidylserine, lysophosphatidic acid and the like (see column 4, lines 6-35 of Illum). The microspheres of Illum are made from materials such as gels, for example starch, gelatin, casein, dextrans, alginate,

agarose, albumin, collagen, chitosan, etc. The instant claims are drawn to microparticles formed of diketopiperazines and drug agents which do not pass into the pulmonary system after nasal administration. Illum does not disclose microparticles comprising diketopiperazines, and the combination of Steiner and Illum does not teach or suggest the nasal administration of microparticles between 10 and 20 microns in size which do not pass into the pulmonary system upon nasal administration.

Therefore, Applicants respectfully assert that Steiner in combination with Illum does not teach or suggest all the claim limitations of pending claims 3, 8, 10, 16, 20 and 21 and request the withdrawal of the rejections on this basis.

CONCLUSION

In light of the foregoing, Applicants respectfully assert that the pending claims are in condition for allowance and that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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